the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality.

REMARKS

A check in the amount of $180 for a Supplemental Information Disclosure Statement is enclosed. Any fees that may be due in connection with the filing of this paper, if the attached check is in the wrong amount, improper or is missing, or with this application during its entire pendency, may be charged to Deposit Account No. 50-1213. If a Petition for an Extension of Time is required, this paper is to be considered such petition.

Claims 1-4, 6-20, 22-28, 44-47, and 53-55 and 57 are presently pending in this application. Claims 5, 21, 48-51 and 56 are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional applications to claim the cancelled subject matter. Claims 1, 20, 23-25 and 57 are amended herein. The amendment finds basis in the specification on page 8, line 13, through page 9, line 3 and claim 5 as originally filed. No new matter has been added.

A Supplemental Information Disclosure Statement also accompanies this Amendment.

RIGHT OF PRIORITY TO U.S. APPLICATION NO. 60/037,165

The Office Action alleges that instant claims 1-28, 44-47, and 53-57 are not entitled to claim priority to provisional application 60/037,165. The Office Action alleges that claims 1-19, 44-47, and 53-57 are drawn to generic composition claims that encompass virtually any and all biopolymers, and in dependent claims, encompass virtually all the nucleic acids as well as antibodies. It is further alleged that the specification defines nucleic acids, enzymes, antibodies, etc., in terms of how they are to function, yet it does not provide an adequate written description of just what these compounds are. Further the Office Action has rejected claims 20-28 because they are allegedly drawn to a method of preparing the composition of claim 1. The Office Action

states that literal supports for certain phraseology can be found in the provisional application but such support is allegedly not sufficient to satisfy to satisfy the written description and enablement requirements of the claimed subject matter. Applicant disagrees with the Examiner's conclusion.

The Instant Claims

Applicant respectfully submits that instant claim 1 is directed to compositions comprising two biopolymers, where a first biopolymer is reversibly linked to an insoluble support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality. Dependent claims 2-4, 6-19, 44-48, and 53-57 further define various components of the composition. Claims 20 and 22-28 are directed to methods of preparing composition of claim 1.

The claimed composition of instant claim 1 is described in the specification of the provisional application in Figures 1 (a) and (c) and on page 2, line 27 through page 3, line 1, as:

> Figure 1 (a) and (c) pictorially depict two general approaches of the invention in which a spacer molecule, A, linked to a polymer support, P, forms a reversible linkage, I, to a nucleic acid or protein/peptide molecule, B, which itself is linked by another reversible linkage, II, to either a nucleic acid, protein/peptide or small molecule (e.g. reporter molecule). Linkage I can be a heterobifunctional trityl group or a hydrophobic interaction stable under aqueous conditions or a photocleavable bond and II can be a bond, which is generated through a chelate complex. The two parts which form the linkage can be reversed (I', II') as shown in (b) and (d).
>
> Figure 2 schematically depicts a nucleic acid molecule, B, which is linked through a spacer, A, via a reversible linkage, I, to a polymer support, P. B interacts via Watson-Crick complementarity with a nucleic acid molecule, C, which in turn through another reversible linkage II allows interaction with a reporter functionality D which can be a protein (enzyme), a nucleic acid or a small detector molecule.

> Figure 3 schematically depicts the same approach as in Figure 2 with the exception that B is linked to the polymer support through a spacer A with a non-reversible linkage.

Further description of the claimed compositions can be found in the specification of the provisional application at page 4, lines 10-17 (detailed description of Figure 1):

> Compound A can be a spacer, a nucleic acid sequence (or nucleic acid analog/mimetic) or a protein or peptide sequence, B can be a nucleic acid (or a nucleic acid analog/mimetic) or a peptide or protein, whereas C can be nucleic acid (or a nucleic acid analog/mimetic), protein/peptide or a small reporter molecule. As an example A is a spacer and I is a heterobifunctional trityl group which is coupled to a nucleic acid B; B carries a chelate functionality which interacts with the poly-his tail of a recombinant alkaline phosphatase (his_6-AP), which carries e.g. a sequence of six histidine residues at the C-terminal end of the polypeptide chain.

Biopolymers for use in the claimed compositions are disclosed in the specification of the provisional application at page 5, lines 16-25:

> For use in the instant process, nucleic acids can be either DNA or RNA single stranded or double stranded, DNA/RNA hybrids, DNA containing ribonucleotides and/or dideoxyribonucleotides and RNA containing deoxyribonucleotides containing modified nucleotides as well as nucleic acid mimetics such as PNAs.
>
> As used herein, the terms "protein", "polypeptide" or "peptide" are all used interchangeably to refer to gene products. Proteins can be antibodies, enzymes, receptor molecules; peptides could be of natural or synthetic origin with oligo-his tail, a functionality for hydrophobic interaction, a photocleavable functionality or chelator functionality and displaying different properties such as being adhesive or representing specific ligand-receptor or specific protease cleavage sites.

Applicant respectfully submits that recitation of any specific biopolymers in the specification is not necessary because it is the particular linked arrangement of biopolymers that constitutes the claimed subject matter of the instant claims. Any biopolymer that is modified to form reversible linkages within the scope of the instant claims can be used. The specification as

discussed above, recites exemplary biopolymers and introduction of functionalities in the biopolymers that can form the reversible linkages of the instant claims. Furthermore, it is not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge. From the description in the specification and the knowledge available in the art, a skilled artisan would be able to recognize what biopolymers can be used to form reversible linkages within the scope of the instant claims. To evidence this, exemplary publications, reporting the use of several biopolymers capable of forming reversible linkages, before the filing date of the provisional application, are discussed below:

WO 96/29431 describes **nucleic acid molecules as biopolymers** that form a photocleavable bond such as a charge transfer complex or a labile bond formed between relatively stable organic radicals as a **reversible linkage in DNA sequencing.**

U.S Patent No. 5,410,068, describes **nucleosides, nucleotides, oligonucleotides, nucleic acids, amino acids, peptides, proteins, monosaccharides, oligosaccharides, carbohydrades, steroids, lipids or alkaloids as biopolymers capable of forming reversible heterobifunctional trityl linkages** for use in polymerase catalyzed extension reaction.

Leikauf *et al.*, *Tetrahedron*, **1995**, 51(13), 3793-3802, describes **nucleic acids as biopolymers** which form reversible heterobifunctional trityl linkages for use in the recovery of nucleic acids after labeling and immobilization.

Blum *et al.*, *J. Biochem. Biophys. Methods*, **1994**, 29, 113-121, have reported the use of histidine-tagged **restriction enzyme as a biopolymer** to form reversible linkage in enzyme purification.

Hochuli *et al.*, *Methods: A Companion to Methods in Enzymalogy*, **1992**, 4, 68-72, have reported histidine-tagged **recombinant proteins and enzymes as biopolymers** that form reversible linkage through chelate complex in affinity purification of proteins.

Smith *et al.*, *The J. Biol. Chem.*, **1988**, 263 (15), 7211-7215, have used **recombinant proteins as biopolymers** in purification of proteins using reversible linkages.

The use of reversible linkers in DNA sequencing where **nucleic acids are used as biopolymers** is disclosed in WO 94/21822.

Therefore, it is evident that a person of skill in the art, based on the disclosure of the provisional application and the knowledge available in the art, would be able to choose appropriate biopolymers for use in the claimed compositions. Applicant respectfully submits that since the specification discloses several exemplary embodiments where various biopolymers are used in the claimed compositions and the knowledge in the art allows a person of skill in the art to choose several more biopolymers capable of forming reversible linkages within the scope of the claimed composition, the specification of the provisional application provides adequate written description for the biopolymers used in the instant claims.

Further, the specification of the provisional application discloses introduction of functionalities in exemplary biopolymers which can form reversible linkages within the scope of the claimed compositions, for example see the specification of the provisional application on page 6, line 39 through page 7, line 12, where introduction of his_6 tail in Bacterial Alkaline Phosphatase (BAP) via inverse PCR and its further conjugation with a chelate modified nucleic acid is illustrated:

> A modified BAP derived from E. coli was genetically designed with a his_6 tail at its carboxy terminus. The his_6 tail was introduced using inverse PCR by which six histidine codons followed by a stop codon were placed at the 3' end of the gene (E. Blum et al. (1994) *Biochem Biophys J.* 29, 113-121). To achieve high expression levels of the recombinant enzyme in E. coli, the region coding for the signal peptide of AP together with the untranslated 5' and 3' regions were exchanged with homologous sequences from the E. coli ompA gene. The expression of the resulting protein construct was under the control of the IPTG (β-D-isopropyl-thio-galactoside) inducible ptac-promoter.

> The BAP-his_6 synthesized in the E.coli cell can easily be isolated from an unpurified cell extract through affinity chromatography using commercially available Ni-NTA resins (Qiagen) to which it forms a strong and specific chelate complex via its his_6 tail. The modified enzyme is therefore now available in high yields, high purity and reproducible batch-to-batch quality. As part of the inventive process, BAP-his_6 is able to form with chelate-modified nucleic acids, a stable complex which for the first time makes available specific conjugates between proteins (here BAP) and nucleic acids in a reproducible 1:1 stoichiometry.

Functionalization of nucleic acid molecules by enzymatic processes (instant claims 25-28) is described on page 7, line 38, through page 8, line 8:

> The chelator and oligoimidazolyl functionalities can also be introduced in high molecular weight nucleic acids using either DNA dependent DNA or RNA polymerases or RNA dependent DNA polymerases using appropriately modified nucleoside triphosphates (either NTPs, 2'-dNTP, 3'-dNTPs, ddNTPs) as depicted in Figure 11. The base will carry either the chelator or the oligoimidazoyl functionality (Figure 12) in case of pyrimidine bases at C5 and in case of purine bases at C8 so that Watson-Crick base pairing is possible. Using the appropriate nucleoside triphosphates those functionalities can either be introduced internally (NTP for RNA synthesis or 2'-dNTP for DNA synthesis) or at the 3'-end (3'-dNTP for RNA synthesis, ddNTP for DNA synthesis). The incorporation can be performed during amplification procedures such as PCR, SDA or during DNA sequencing. Those skilled in the art will realize other approaches to introduce either chelator or oligo-imidazolyl moieties into nucleic acids.

Modified nucleoside triphosphates for use in enzymatic introduction of the chelator or imidazolyl functionalities in the nucleic acid during amplification procedures such as Polymerase Chain Reaction or Strand Displacement Amplification are disclosed in figures 11-12.

The reversible linkages in the instant claims are described in the provisional application at, for example, Figures 1 (a)-(c) and page 2, lines 27-34, which recite:

> Figure 1 (a) and (c) pictorially depict two general approaches of the invention in which a spacer molecule, A, linked to a polymer support, P, forms a reversible linkage, I, to a nucleic acid or protein/peptide molecule,

> B, which itself is linked by another reversible linkage, II, to either a nucleic acid, protein/peptide or small molecule (e.g. reporter molecule). Linkage I can be a **heterobifunctional trityl group** or a hydrophobic interaction stable under aqueous conditions or a photocleavable bond and II can be a bond, which is generated through **a chelate complex**. The two parts which form the linkage can be reversed (I', II') as shown in (b) and (d).

Further, on page 4, lines 10-17, and line 24 through page 5, line 4, the specification of the provisional application discloses:

> Compound A can be a spacer, a nucleic acid sequence (or nucleic acid analog/mimetic) or a protein or peptide sequence, B can be a nucleic acid (or a nucleic acid analog/mimetic) or a peptide or protein, whereas C can be nucleic acid (or a nucleic acid analog/mimetic), protein/peptide or a small reporter molecule. As an example A is a spacer and I is a **heterobifunctional trityl group** which is coupled to a nucleic acid B; B carries a **chelate functionality** which interacts with the poly-his tail of a recombinant alkaline phosphatase (his_6-AP), which carries e.g. a sequence of six histidine residues at the C-terminal end of the polypeptide chain.
>
> Figure 2 shows schematically how amplification (e.g. polymerase chain reaction (PCR) or ligase chain reaction (LCR) products B-C can be captured specifically, purified and subsequently detected on the support or in solution. The first reversible linkage I (or I') e.g. **a heterobifunctional trityl group** anchors one strand of the LCR or PCR product via a spacer A to the support through an acid labile tritylether bond the precursor of which has been introduced by an appropriately functionalized primer during the LCR or PCR reaction. The strand C carries e.g. the **chelate functionality** also introduced by using an appropriately functionalized primer during PCR or LCR. The chelated moiety can then interact with a reporter functionality e.g. his_6-AP for subsequent detection and quantification of amplification product. B can also be a cDNA molecule which can be linked through its 5'-end to the polymer support. With appropriate primers, solid phase DNA sequencing can be performed. Considering an array format, this could be used for high throughput genetic and expression profiling experiments.

Therefore, reversible linkages within the scope of the instant claims are adequately described in the provisional application.

Further, the solid supports (as claimed in instant claims 6-10) are described in the provisional application on page 4, lines 1-9. The specification discloses:

> the solid supports can be flat such as membranes, glass plates, metals, plastic films and composites thereof with a homogeneously functionalized surface or functionalized to result in an array format including flat supports with pits, wells, combs, microtiter plates, microtiter filter plates; flat supports can also be magnetic or with an array shaped (checkered) magnetic field; solid supports can also be used as beads from different plastic materials, inorganic supports such as silica, CPG (Controlled Pore Glass), metal, different polymeric material, cellulose, Sephadex, Sepharose; the beads can be porous or non-porous, of different diameter and magnetic or non-magnetic. Also a combination of beads in the pits/wells of flat supports thus forming an array format can be employed.

Claims 6-10 in the provisional application also disclose the subject matter of the instant claims. For example, see below:

> 6. A composition according to claim 1, wherein the insoluble support is selected from the group consisting of: a flat surface, a comb and a bead.
>
> 7. A composition according to claim 6, wherein the insoluble support is selected from the group consisting of: a silicon wafer, glass plate, metal, plastic, film and composites thereof with pits or wells.
>
> 8. A composition according to claim 7, wherein the biopolymer is conjugated to the insoluble support in an array format.
>
> 9. A composition according to claim 7, wherein the bead is comprised of an inorganic material selected from the group consisting of: silica, Controlled Pore Glass (CPG), plastic, metal, cellulose, Sepharose and Sephadex.
>
> 10. A composition according to claim 6, wherein the insoluble support is comprised of a magnetic or electromagnetic material.

The specific examples recite exemplary insoluble supports such as **beads** (See page 9, example 2), **microtiter filter plates with wells** (See page 9, example 3) and **a membrane derivatize**d with a capture oligo (See page 10, example 4). Thus, the provisional application discloses several exemplary insoluble supports.

Therefore, the provisional application provides adequate written description for the insoluble supports in the instant claims.

The specification of the provisional application also discloses the use of claimed compositions in purification and detection of PCR or LCR products, for example see page 4, line 24 through page 5, line 4, recite:

> Figure 2 shows schematically how e.g. PCR or LCR products B-C can be captured specifically, purified and subsequently detected on the support or in solution. The first reversible linkage I (or I') e.g. a heterobifunctional trityl group anchors one strand of the LCR or PCR product via a spacer A to the support through an acid labile tritylether bond the precursor of which has been introduced by an appropriately functionalized primer during the LCR or PCR reaction. The strand C carries e.g. the chelate functionality also introduced by using an appropriately functionalized primer during PCR or LCR. The chelated moiety can then interact with a reporter functionality e.g. his_6-AP for subsequent detection and quantification of amplification product. B can also be a cDNA molecule which can be linked through its 5'-end to the polymer support. With appropriate primers, solid phase DNA sequencing can be performed. Considering an array format, this could be used for high throughput genetic and expression profiling experiments. As shown in Figure 2, B could also be a specific (or oligo-dT) capture sequence to fish mRNA. The cDNA can be directly synthesized since the capture sequence simultaneously can act as a primer for the RNA dependent DNA polymerase. The RNA can be removed, the cDNA purified by washing and filtration steps and either released or directly used for subsequent DNA sequencing. It can also be envisioned that the capture sequence while serving as a primer for the RNA dependent DNA polymerase can be used directly to generate sequencing ladders employing ddNTP's as terminators. After purification of the sequencing ladders by washing and filtration, the bond to the polymer support is cleaved and the purified sequencing ladders subjected to either gel electrophoretic or mass spectrometric separation (H. Köster et al., A Strategy for Rapid and Efficient DNA Sequencing by Mass Spectrometry, *Nature Biotech*, (1996) 14, 1123-1128; U.S. Patent No. 5, 547,035 to H. Köster; International Patent Application No. W094/21822 to H. Köster; and International Patent Application No. W096/29431 to H. Köster)

Further, the specification at pages 9-10, Example 3, describes an exemplary method where a composition comprising the first biopolymer (oligonucleotide) reversibly linked (trityl linkage) to the insoluble support

(microtiter filter plate) and a second biopolymer (an enzyme) reversibly (chelate complex) to the first biopolymer is prepared for use in detection of LCR products. The method is also illustrated in figure 13.

The provisional application discloses all the components of the claimed compositions, exemplifies the claimed compositions and also describes their uses. Thus, the provisional application provides adequate written description for the claimed subject matter. Therefore, the pending claims are clearly entitled to the benefit of priority.

REJECTION OF CLAIMS 1-28, 44-47, AND 53-57 UNDER 35 U.S.C. §112, FIRST PARAGRAPH FOR ALLEGED LACK OF WRITTEN DESCRIPTION

Claims 1-28, 44-47, and 53-57 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A). Claims 1-19, 44-47 and 53-57

The Office Action states that claims 1-19, 44-47, and 53-57 are drawn to compositions that are comprised of biopolymers which are further defined in dependent claims as enzymes, nucleic acids (DNA, RNA, analogs or mimetics of DNA or RNA), antibodies, and polypeptides, and that these biopolymers are bound to various supports, be it inorganic, insoluble, magnetic, etc., and that there are various reversible linkages used to bind the biopolymers to the supports. The Office Action alleges that the aspect of defining a biopolymer as being a nucleic acid (including DNA, RNA, analogs or mimetics of DNA or RNA), as well as being a polypeptide etc., does not satisfy the written description requirement. It is urged in the Office action that it is not enough that certain undisclosed embodiments may be obvious when the disclosure is coupled with what was known in the art at the time of filing, the specification must provide an adequate written description of the claimed subject matter. Applicant

respectfully submits that the grounds for this rejection are rendered moot with respect to claims 5 and 56, which have been cancelled herein. This rejection is respectfully traversed with respect to the pending claims.

Relevant Law

The purpose behind written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description, has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is

whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

The guidelines promulgated by the U.S. PTO embody these rules:

> In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:
>
> (1) identify the claim limitation not described; and
>
> (2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

in this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

The Instant Claims

Instant claim 1 is directed to compositions comprising two biopolymers, where a first biopolymer is reversibly linked to an insoluble support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality. Dependent claims 2-4, 6-19, 44-47, and 53-57, further define various components of the composition.

Analysis

Applicant respectfully submits that the application discloses exemplary embodiments of the claimed compositions in Figures 1, 2, 3, 6 and 7. The specification on paragraphs beginning on page 2, line 14, through page 3, line 1, of the application describes the claimed compositions:

> Figure 1 (a) and (c) pictorially depict two general approaches of the invention in which a spacer molecule, A, linked to a polymer support, P, forms a reversible linkage, I, to a nucleic acid or protein/peptide molecule, B, which itself is linked by another reversible linkage, II, to either a nucleic acid, protein/peptide or small molecule (e.g. reporter molecule). Linkage I can be a heterobifunctional trityl group or a hydrophobic interaction stable under aqueous conditions or a photocleavable bond and II can be a bond, which is generated through a chelate complex. The two parts which form the linkage can be reversed (I', II') as shown in (b) and (d).
>
> Figure 2 schematically depicts a nucleic acid molecule, B, which is linked through a spacer, A, via a reversible linkage, I, to a polymer support, P. B interacts via Watson-Crick complementarity with a nucleic acid molecule, C, which in turn through another reversible linkage II allows interaction with a reporter functionality D which can be a protein (enzyme), a nucleic acid or a small detector molecule.
>
> Figure 3 schematically depicts the same approach as in Figure 2 with the exception that B is linked to the polymer support through a spacer A with a non-reversible linkage.

Further description of the claimed compositions can be found in the specification at page 6, lines 1-8 (detailed description of Figure 1):

> Compound A can be a spacer, a nucleic acid sequence (or nucleic acid analog/mimetic) or a protein or peptide sequence, B can be a nucleic acid (or a nucleic acid analog/mimetic) or a peptide or protein, whereas C can be nucleic acid (or a nucleic acid analog/mimetic), protein/peptide or a small reporter molecule. As an example A is a spacer and I is a heterobifunctional trityl group which is coupled to a nucleic acid B; B carries a chelate functionality which interacts with the poly-his tail of a recombinant alkaline phosphatase (his_6-AP), which carries e.g. a sequence of six histidine residues at the C-terminal end of the polypeptide chain.

The specification discloses exemplary biopolymers for use in the claimed compositions at page 5, lines 12-16:

> As shown in Figure 1, two different reversible linkages I and II (a,c), which could be positioned with their functionalities reversed (I',II'; b, d) are used to link "biomolecules" or "biopolymers" (i.e.organic molecules, including nucleic acids, peptides, polypeptides) to an insoluble support.

Further biopolymers for use in the claimed compositions are disclosed in the specification at page 7, line 18 through page 8, line 9:

> For use in the instant process, nucleic acids can be single stranded or double stranded polynucleotides (including oligonucleotides), whether natural or synthetic, such as deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) or DNA/RNA hybrids, DNA containing ribonucleotides and/or dideoxyribonucleotides and RNA containing deoxyribonucleotides. Also encompassed by the term "nucleic acid" are modified nucleotides (e.g. phosphorothioate modified) as well as nucleic acid mimetics or analogs, such as peptide nucleic acids (PNAs).
>
> As used herein, the terms "protein", "polypeptide" or "peptide" are all used interchangeably to refer to gene products. Proteins can be antibodies, enzymes, receptor molecules; peptides could be of natural or synthetic origin with oligo-his tail, a functionality for hydrophobic interaction, a photocleavable functionality or chelator functionality and displaying different properties such as being adhesive or representing specific ligand-receptor or specific protease cleavage sites.

As discussed above, applicant respectfully submits that recitation of any specific biopolymers in the specification is not necessary because it is the

particular linked arrangement of biopolymers that constitutes the claimed subject matter of the instant claims. Any biopolymer that is modified to form reversible linkages within the scope of the instant claims can be used. The specification recites exemplary biopolymers and introduction of functionalities in the biopolymers that can form the reversible linkages of the instant claims. Furthermore, it is not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge. From the description in the specification and the knowledge available in the art, a skilled artisan would be able to recognize what biopolymers can be used to form reversible linkages within the scope of the instant claims. Applicant respectfully submits that since the specification discloses several exemplary embodiments where various biopolymers are used in the claimed compositions and the knowledge in the art allows a person of skill in the art to choose several more biopolymers capable of forming reversible linkages within the scope of the claimed composition, the specification provides adequate written description of biopolymers for use in the claimed compositions.

The specification discloses various insoluble supports on page 5, lines 17-26 and reversible linkages on page 3, lines 14-21 and page 6, lines 1-8, discussed in detail below. The specification also discloses the use of claimed compositions in purification and detection of PCR or LCR products, for example see page 6, lines 15-27 recite:

> Figure 2 shows schematically how amplification (e.g. polymerase chain reaction (PCR) or ligase chain reaction (LCR) products B-C can be captured specifically, purified and subsequently detected on the support or in solution. The first reversible linkage I (or I') e.g. a heterobifunctional trityl group anchors one strand of the LCR or PCR product via a spacer A to the support through an acid labile tritylether bond the precursor of which has been introduced by an appropriately functionalized primer during the LCR or PCR reaction. The strand C carries e.g. the chelate functionality also introduced by using an appropriately functionalized primer during PCR or LCR. The chelated moiety can then interact with a reporter functionality e.g. his_6-AP for subsequent detection and quantification of amplification product. B can also be a cDNA molecule

which can be linked through its 5'-end to the polymer support. With appropriate primers, solid phase DNA sequencing can be performed. Considering an array format, this could be used for high throughput genetic and expression profiling experiments.

Therefore, the specification provides adequate description of the claimed subject matter by describing all the components of the claimed compositions, exemplifing the claimed compositions and describing the uses of claimed compositions.

B). Claims 6-8

Claims 6, 7 and 8 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of compositions where all or "even some" of the claimed elements of the insoluble support are combined. The Office Action notes that an insoluble support is defined in claim 6 as being selected from a group consisting of flat surface, a microtiter plate, a comb, and a bead. It is noted that the supports are further defined in claim 7 as being a silicon wafer, glass plate, metal, plastic, film, and composites thereof with pits or wells which are further defined as comprising inorganic material selected from the group consisting of silica, controlled pore glass (CPG), plastic, metal, cellulose, agarose and dextran cross-linked with epichlorohydrin (claim 8). The Office Action alleges that a bead of some undisclosed type is contemplated for use in example 3 and that the suggestion in prophetic example does not reasonably suggest that applicant was in possession of the genus of compositions now being claimed. Applicant respectfully traverses this rejection.

Relevant Law

As discussed above.

Instant Claims

Claim 6 depends from claim 1 and defines insoluble supports used in the compositions of claim 1 as being selected from a group consisting of flat surface, a microtiter plate, a comb, and a bead. The insoluble supports are further defined in claim 7 as being a silicon wafer, glass plate, metal, plastic,

film, and composites thereof with pits or wells. Claims 8 and 9 further define the insoluble supports.

Analysis

Applicant respectfully submits that as discussed in the previous response, the "insoluble supports" are described in the specification on page 5, lines 17-26. The specification discloses:

> the insoluble supports can be flat such as membranes, glass plates, metals, plastic films and composites thereof with a homogeneously functionalized surface or functionalized to result in an array format including flat supports with pits, wells, combs, microtiter plates, microtiter filter plates; flat supports can also be magnetic or with an array shaped (checkered) magnetic field; solid supports can also be used as beads from different plastic materials, inorganic supports such as silica, GPG (Controlled Pore Glass), metal, different polymeric material, cellulose, Sephadex, Sepharose; the beads can be porous or non-porous, of different diameter and magnetic or non-magnetic. Also a combination of beads in the pits/wells of flat supports thus forming an array format can be employed.

Claims 6-10 in the application as originally filed, disclose the subject matter of the instant claims. For example, see below:

> 6. A composition according to claim 1, wherein the insoluble support is selected from the group consisting of: a flat surface, a comb and a bead.
>
> 7. A composition according to claim 6, wherein the insoluble support is selected from the group consisting of: a silicon wafer, glass plate, metal, plastic, film and composites thereof with pits or wells.
>
> 8. A composition according to claim 7, wherein the biopolymer is conjugated to the insoluble support in an array format.
>
> 9. A composition according to claim 7, wherein the bead is comprised of an inorganic material selected from the group consisting of: silica, Controlled Pore Glass (CPG), plastic, metal, cellulose, Sepharose and Sephadex.
>
> 10. A composition according to claim 6, wherein the insoluble support is comprised of a magnetic or electromagnetic material.

The specific examples recite exemplary insoluble supports such as **beads** (See page 15, example 2), **microtiter filter plates with wells** (See page 15, example 3) and **a membrane derivatize**d with a capture oligo (See page 16, example 4). Thus, the application as originally filed discloses the genus of composition for the claimed insoluble supports. Applicant respectfully submits that the allegation that the suggestion in prophetic example does not reasonably suggest that applicant was in possession of the genus of compositions now being claimed is irrelevant because it is not necessary to make and test all or any embodiments to meet written description requirement. Furthermore, as discussed above, specific examples in the application recite exemplary insoluble supports and claims 6-10 as originally filed, disclose the genus of compositions being claimed. The Examiner is reminded that possession does not mean physical possession but appreciation. The Examiner is further reminded that the guidelines promulgated by the U.S. PTO for lack of written description rejection embody following rules:

> In rejecting a claim, set forth express findings of fact which support the lack of written description conclusion. These findings should:
>
> (1) identify the claim limitation not described; and
>
> (2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.

In this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of insoluble supports as claimed in claims 6 and 7 in view of the disclosure of the application as filed. Therefore, the specification provides adequate written description where all of these requisite elements are combined and there is no basis to conclude that the applicant was not in possession of the genus of compositions being claimed.

C). Claims 20-28

Claims 20-28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not set forth in sufficient detail the method of claims 20-28, whereby one is to produce the compositions encompassed by claim 1. The Office Action notes that the claimed method requires one to utilize various first and second reversible linkages formed through a trityl derivative, chelate complex, a hydrophobic interaction or a photocleavable functionality. It is further noted that other claims require that an enzymatic process is used to introduce functionalities into nucleic acids and that this enzymatic process is part of a nucleic acid sequencing reaction. The Office Action alleges that a review of the specification fails to find where such methods are described even in the context of a prophetic example. The Office Action further alleges that the examples and guidance provided is found, at best, to only indirectly suggest or make obvious the claimed methods and that it does not satisfy the written description requirement. It is respectfully submitted that the grounds for this rejection are rendered moot with respect to claim 21, which has been cancelled herein. This rejection is respectfully traversed with respect to the pending claims.

Relevant Law

As discussed above.

The Instant Claims

Applicant respectfully submits that amended claim 20 depends from claim 1 and is directed to producing the composition of claim 1 comprising two biopolymers, where a first biopolymer is reversibly linked to an insoluble support and a second biopolymer is reversibly linked to the first biopolymers, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality. Claim 22 further define the reversible linkage between the first and the second biopolymer as a chelate

complex. Claims 23-28 further describe introduction of various functionalities into the biopolymers to form the reversible linkages.

Relevant Law

As discussed above.

Analysis

Compositions produced by the claimed methods wherein the first reversible linkage is trityl linkage and second reversible linkage is selected from a chelate complex and a photocleavable functionality, are disclosed in the specification. For example, see Figures 1 (a)-(c) and page 3, lines 14-21 which recite:

> Figure 1 (a) and (c) pictorially depict two general approaches of the invention in which a spacer molecule, A, linked to a polymer support, P, forms a reversible linkage, I, to a nucleic acid or protein/peptide molecule, B, which itself is linked by another reversible linkage, II, to either a nucleic acid, protein/peptide or small molecule (e.g. reporter molecule). Linkage I can be a **heterobifunctional trityl group** or a hydrophobic interaction stable under aqueous conditions or a photocleavable bond and II can be a bond, which is generated through **a chelate complex**. The two parts which form the linkage can be reversed (I', II') as shown in (b) and (d).

Further, on page 6, lines 1-8 and lines 15-27 the specification discloses:

> Compound A can be a spacer, a nucleic acid sequence (or nucleic acid analog/mimetic) or a protein or peptide sequence, B can be a nucleic acid (or a nucleic acid analog/mimetic) or a peptide or protein, whereas C can be nucleic acid (or a nucleic acid analog/mimetic), protein/peptide or a small reporter molecule. As an example A is a spacer and I is a **heterobifunctional trityl group** which is coupled to a nucleic acid B; B carries a **chelate functionality** which interacts with the poly-his tail of a recombinant alkaline phosphatase (his_6-AP), which carries e.g. a sequence of six histidine residues at the C-terminal end of the polypeptide chain.
>
> Figure 2 shows schematically how amplification (e.g. polymerase chain reaction (PCR) or ligase chain reaction (LCR) products B-C can be captured specifically, purified and subsequently detected on the support or in solution. The first reversible linkage I (or I') e.g. **a heterobifunctional trityl group** anchors one strand of the LCR or PCR product via a spacer A to the support through an acid labile tritylether bond the precursor of which has been introduced by an appropriately functionalized primer

during the LCR or PCR reaction. The strand C carries e.g. the **chelate functionality** also introduced by using an appropriately functionalized primer during PCR or LCR. The chelated moiety can then interact with a reporter functionality e.g. his_6-AP for subsequent detection and quantification of amplification product. B can also be a cDNA molecule which can be linked through its 5'-end to the polymer support. With appropriate primers, solid phase DNA sequencing can be performed. Considering an array format, this could be used for high throughput genetic and expression profiling experiments.

Further, the specification discloses introduction of functionalities capable of forming the reversible linkages in the biopolymers. For example, the introduction of his_6 tail in Bacterial Alkaline Phosphatase (BAP) via inverse PCR and its further conjugation with a chelate modified nucleic acid is described on page 11, lines 1-16,:

A modified BAP derived from E. coli was genetically designed with a his_6 tail at its carboxy terminus. The his_6 tail was introduced using inverse PCR by which six histidine codons followed by a stop codon were placed at the 3' end of the gene (E. Blum et al. (1994) *Biochem Biophys J.* 29, 113-121). To achieve high expression levels of the recombinant enzyme in E. coli, the region coding for the signal peptide of AP together with the untranslated 5' and 3' regions were exchanged with homologous sequences from the E. coli ompA gene. The expression of the resulting protein construct was under the control of the IPTG (β-D-isopropyl-thio-galactoside) inducible ptac-promoter.

The BAP-his_6 synthesized in the E.coli cell can easily be isolated from an unpurified cell extract through affinity chromatography using commercially available Ni-NTA resins (Qiagen) to which it forms a strong and specific chelate complex via its his_6 tail. The modified enzyme is therefore now available in high yields, high purity and reproducible batch-to-batch quality. As part of the inventive process, BAP-his_6 is able to form with chelate-modified nucleic acids, a stable complex which for the first time makes available specific conjugates between proteins (here BAP) and nucleic acids in a reproducible 1:1 stoichiometry.

Functionalization of nucleic acid molecules by enzymatic processes (claims 25-28) is described on page 11, line 21, through page 12, line 25:

The chelator and oligoimidazolyl functionalities can also be introduced in high molecular weight nucleic acids using either DNA dependent DNA or RNA polymerases or RNA dependent DNA

polymerases using appropriately modified nucleoside triphosphates (either NTPs, 2'-dNTP, 3'-dNTPs, ddNTPs) as depicted in Figure 11. The base will carry either the chelator or the oligoimidazoyl functionality (Figure 12) in case of pyrimidine bases at C5 and in case of purine bases at C8 so that Watson-Crick base pairing is possible. Using the appropriate nucleoside triphosphates those functionalities can either be introduced internally (NTP for RNA synthesis or 2'-dNTP for DNA synthesis) or at the 3'-end (3'-dNTP for RNA synthesis, ddNTP for DNA synthesis). The incorporation can be performed during amplification procedures such as PCR, SDA or during DNA sequencing. Those skilled in the art will realize other approaches to introduce either chelator or oligo-imidazolyl moieties into nucleic acids.

Modified nucleoside triphosphates for use in enzymatic introduction of the chelator or imidazolyl functionalities in the nucleic acid during amplification procedures such as Polymerase Chain Reaction or Strand Displacement Amplification are disclosed in figures 11-12. Further, the specification at page 15, Example 3, describes an exemplary method where a composition comprising the first biopolymer (oligonucleotide) reversibly linked (trityl linkage) to the insoluble support (microtiter filter plate) and a second biopolymer (an enzyme) reversibly (chelate complex) to the first biopolymer is prepared for use in detection of LCR products. The method is also illustrated in figure 13. Thus the claimed methods are described in the specification. Therefore, the allegation that the examples and guidance provided is found, at best, to only indirectly suggest or make obvious the claimed methods is without any basis.

Rebuttal to Specific Arguments in the Office Action

1). Biopolymers that would work Vs. biopolymers that have no functionality

The Office Action alleges that the applicant is seeking to claim the universe of biopolymers that, at a minimum are bipartite. It is further urged that the applicant has not provided an adequate written description of all of the nucleic acids and polypeptides and receptors that exist in the world, yet the claims encompass such. The Office Action alleges that the specification has not

been found to provide an adequate written description of those biopolymers that would work over those that have no functionality.

Applicant respectfully submits that the specification, as discussed above, discloses several exemplary biopolymers, including but not limited to, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), DNA/RNA hybrids, DNA containing ribonucleotides and/or dideoxyribonucleotides, RNA containing deoxyribonucleotides, modified nucleotides (e.g. phosphorothioate modified) and nucleic acid mimetics or analogs, such as peptide nucleic acids (PNAs). The knowledge available in the art provides several more biopolymers. Applicant respectfully submits that it is the particular linked arrangement of biopolymers and not any specific biopolymer that constitutes the claimed subject matter. As discussed above, the specification discloses introduction of functionalities in exemplary biopolymers which then form reversible linkages within the scope of the claims. Further, the Examiner is reminded that it is not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge. It is not necessary to list all the biopolymers that can be used in the claimed compositions because such biopolymers and their structures are known in the art. Therefore, based on the disclosure in the application and in the art, a skilled artisan would be able to determine which biopolymers can be used to form reversible linkages within the scope of the instant claims.

2). Claims limited to biopolymers that could be simply DNA or proteins

The Office Action alleges that for the purpose of examination the claim limitation "the reversible linkage between the first and second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality" has been interpreted as encompassing those steps that could be used in the synthesis of any two biopolymers and that the "reversible linkage" is the normal affinity that one biopolymer has for another, e.g., complementary strands of nucleic acids, the binding of an antibody to an antigen, or the binding

of a receptor to a ligand. It is further alleged that with this interpretation the claims are limited to biopolymers that could be simply DNA or proteins.

Applicant respectfully submits that instant claim 1 clarifies the scope of the reversible linkages by reciting:

A compositions comprising two biopolymers, where a first biopolymer is reversibly linked to an insoluble support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality.

Therefore, the biopolymers contemplated in instant claim 1 are not limited to simply DNA or proteins but encompass any biopolymer that is capable of forming a reversible linkage within the scope of the claimed composition.

3). Product by process claim

The Office Action alleges that the third clause of claim 1 could be construed a product-by-process claim and the disclosure does not support the position that the genus of claimed biopolymers has been adequately described. It is further urged that it not possible to differentiate between those biopolymers produced by the claimed method over those that have been produced by another method. The Office Action alleges that one prophetic example does not reasonably suggest that applicant was in possession of the genus of biopolymers claimed.

Applicant respectfully submits that as amended herein, claim 1 clarifies that it not a product by process claim. As discussed above, the composition of claim 1 is adequately disclosed in the application. Applicant respectfully submits that the assertion in the Office Action that "it not possible to differentiate between those biopolymers produced by the claimed method over those that have been produced by another method" is wrong because the claims are not directed towards making biopolymers. The claims are directed towards

compositions containing particular linked arrangements of biopolymers and the application provides description of how to make such compositions. Further, the allegation that the suggestion in prophetic example does not reasonably suggest that applicant was in possession of the genus of biopolymers claimed is irrelevant because it is not necessary to make and test all or any embodiments to show possession of the claimed subject matter.

4). Identification of possible starting materials does not satisfy the written description requirement

The Office Action notes that the specification provides literal support for various insoluble supports specifically identified in claims 6 and 7. The Office Action alleges that such literal support is considered to provide support for starting materials that could be used in a method of making the biopolymers. The Office Action therefore concludes that the identification of possible starting materials, however does not satisfy the written description requirement so as to reasonably suggest that applicant was in possession of the claimed genera of compositions.

As discussed above, the specification satisfies the written description requirement as it applies to the claimed composition of claim 1. Claims 6 and 7 further claim various insoluble supports for use in these compositions. The Office Action acknowledges that the insoluble supports claimed in claims 6 and 7 have literal support in the specification. Applicant further notes that the specification provides exemplary embodiments where insoluble supports such as beads (See page 15, example 2), microtiter filter plates with wells (See page 15, example 3) and a membrane derivatized with a capture oligo (See page 16, example 4) are used as insoluble supports in the claimed compositions. Therefore, applicant respectfully submits that based on these examples a skilled artisan would know how to use other insoluble supports. The use of insoluble supports is a matter of routine practice in the art. As discussed above, the specification provides adequate written description of the various components in

the claimed compositions, e.g., first and second biopolymers, reversible linkages and insoluble supports. The specification discloses how to use exemplary components to arrive at the claimed compositions. Therefore, the allegation that identification of the starting materials does not satisfy the written description requirement is without merit. Examiner is reminded that it is not necessary to include in the specification that which those of skill in the art know. Therefore, applicant respectfully submits that applicant had possession of the claimed subject matter.

5). Incorporation by reference of the cited articles

The Office Action refers to pages 17-19 of the previous response where applicant provided arguments in support of the written description requirement and further to pages 23-24 of applicant's previous response wherein applicant has cited several references to support the argument that the specification is enabling. The Office Action alleges that applicant has not shown that any of the documents have been incorporated by reference.

Applicant draws Examiner's attention to page 23, line 20, in the previous response, where it is mentioned that "the following articles were cited in the specification". Applicant further refers Examiner to page 14, lines 3-5, of the specification which recites:

> The entire contents of all cited references (including literature references, issued patents, published patent applications and co-pending patent applications, as cited throughout this application) are hereby expressly incorporated by reference.

Therefore, the articles are properly incorporated by reference in the application.

6). Modification of prior art methods

The Office Action further alleges that the specification is silent as to how the prior art methods are to be modified such that the non-obvious compositions and methods are fully described and enabled.

The arguments in the Office Action appear to have been made under the assumption that the references in the previous response were cited to support the arguments for the written description requirement. Applicant respectfully submits that the references were cited to provide evidence in response to the enablement rejection in the previous Office Action as it applied to the enablement of use of the claimed compositions. The references were cited to show the art for use of reversibly linked biopolymers. None of the references cited in the previous response were provided in support of the written description requirement. Applicant respectfully brings it the Examiner's attention that the references were not cited to provide prior art methods that can be modified to arrive at claimed compositions or methods. They were provided in support of the argument that at the time of the effective filing date of this application and before, a skilled artisan knew how to use reversibly linked biopolymers in DNA sequencing, DNA diagnostics, nucleic acid amplification, Polymerase and Ligase Chain Reactions (PCR, LCR), hybridization experiments and solid phase biochemistry. Therefore, the allegation that the specification is silent as to how the prior art methods are to be modified such that the non-obvious compositions and methods are fully described and enabled is irrelevant.

REJECTION OF CLAIMS 1-28, 44-47, AND 53-57 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH FOR ALLEGED LACK OF LACK OF ENABLEMENT

Claims 1-28, 44-47, and 53-57 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action states that aside from providing an adequate written description of the invention, the specification must also enable the use of the invention. The Office Action alleges that as presently worded the claims encompass a vast multitude of compositions yet the specification does not set forth in sufficient detail just how one is to differentiate between those embodiments that work and those that will not work. It is further alleged that

the specification does not teach in sufficient detail how to use the multitudinous compositions disclosed in the specification, in any of the claimed methods, much less enable all the compositions in all the methods. Applicant respectfully traverses this rejection.

Relevant Law

It is incumbent upon the examiner to first establish a prima facie case of non-enablement. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.)

Id. (emphasis in original); See also Fiers v. Revel, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, Gould v. Mossinghoff, 229 USPQ 1, 13 (D.D.C. 1985), aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. § 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct").

In order to satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be

satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without **undue** experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all

the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against **the claimed subject matter**. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect to scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

The Instant Claims

Claim 1 is directed to a composition, comprising two biopolymers, wherein, the first biopolymer is linked to an insoluble support by a reversible linkage; and the second biopolymer is linked to the first biopolymer by a reversible linkage, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality.

Dependent claims 2-4, 11, 12, 17-19, 44, and 53-56 further define the biopolymers. Dependent claims 8, 13-16, 45, and 56 further define the reversible linkages. Dependent claims 6, 7, 9, 10, and 45-47 further define the insoluble support. Claims 20, 22-28 are directed to methods for preparing the claimed compositions.

Analysis

Applying the above factors to the instant claims, applicant respectfully submits that, as described in detail below, it would not require undue experimentation to practice the full scope of the claimed subject matter.

Scope of the claims

The compositions in the instant application contain specific elements that are described and taught in the specification. Various linked arrangements of biopolymers in the claimed compositions are exemplified, for example, in Figures 1-3. The specification defines all the components in the compositions, for example, biopolymers are defined on page 5, lines 12-16, as organic molecules, including nucleic acids, peptides and polypeptides; various insoluble supports for use in claimed compositions are described in the specification (see page 5, lines 17-26); exemplary reversible linkages in the claimed compositions, including but not limited to, heterobifunctional trityl linkers between the insoluble support and the first biopolymer and chelate complexes and photocleavable functionalities between the first and the second biopolymer are disclosed in the specification (see, *e.g.*, page 3, lines 18-20, page 4, lines 3-4, page 8, lines 13-15 and 21-27, and page 9, lines 1-18). The specification, including the working examples, describes how to make the compositions. Therefore claims 1-28, 44-47 and 53-56 are directed to compositions and methods for preparing these compositions, that are described in the specification. Thus the instant claims are not overly broad as compared to the scope of the disclosure.

The level of skill in the art is high

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art.

Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, the skilled artisan knew the use of reversibly linking biopolymers in DNA sequencing, DNA diagnostics, nucleic acid amplification, Polymerase and Ligase Chain Reactions (PCR, LCR), hybridization experiments and solid phase biochemistry as evidenced by a large body of literature directed to the use of reversibly linked biopolymers.

The articles cited in the specification, of record and attached hereto, describe reversible linkages and their uses in various applications. For example, use of **reversibly linked biomolecules in DNA sequencing** is disclosed in WO 96/29431. The patent describes the use of photocleavable bond such as a charge transfer complex or a labile bond formed between relatively stable organic radicals as reversible linkages in DNA sequencing. The patent describes **nucleic acid molecules as biopolymers.**

U.S Patent No. 5,410,068, describes reversible immobilization of compounds with a triphenylmethyl group as a linking agent for use in **polymerase catalyzed extension reaction. The biopolymers capable of forming reversible linkages are also disclosed and include nucleoside, nucleotide, oligonucleotide, nucleic acid, amino acid, peptide, protein, monosaccharide, oligosaccharide, carbohydrate steroid, lipid or alkaloid.**

Leikauf *et al.*, *Tetrahedron*, **1995**, 51(13), 3793-3802, describes use of **heterobifunctional trityl derivatives as reversible linking agents for the recovery of biopolymers (nucleic acids)** after labeling and immobilization.

Blum *et al.*, *J. Biochem. Biophys. Methods*, **1994**, 29, 113-121, have reported the use of **reversible linkage in enzyme purification and describe restriction enzyme as a biopolymer** .

Hochuli *et al.*, *Methods: A Companion to Methods in Enzymalogy*, **1992**, 4, 68-72, have reported the **use of reversible linkage formed through chelate**

complex in affinity purification of proteins. The biopolymers described include **recombinant proteins and enzymes.**

Smith *et al.*, *The J. Biol. Chem.*, **1988**, 263 (15), 7211-7215, have described **purification of proteins using reversible linkages.**

The use of **reversible linkers in DNA sequencing** is disclosed in WO 94/21822.

In addition, a large body of publications, not cited in the application, describe the use of reversible linkages in various applications.

Scoten *et al.*, *Anal. Biochem.*, **1992**, 205, 313-18, have described **reversible immobilization in solid phase biotechnology.**

Penke et al. *J. Chroma.*, **1986**, 376, 307-314, have reported reversible linkages for **targeted immobilization of Neurotransmitters and Neuropeptides.**

Kadonaga *et al.*, *Biochemistry*, **1986**, 83, 5889-5893, have used reversible linkers in **affinity purification of sequence specific DNA binding proteins.**

Cuatrecasas *et al.*, *Biochemistry*, **1968**, 61, 636-643, have used **reversible linkers in enzyme purification** by affinity chromatography.

Köster *et al.* in U.S.patent 5,948,624, have disclosed use of **reversible linkers in DNA sequencing.**

U.S. Patent No. 5,547,835 discloses several examples of functionalities that can form charge transfer complexes and thereby form **reversible linkages for use in DNA sequencing.**

Gildea *et al.*, *Tetrahedron*, **1990**, 31, 7095-98, have reported triphenylmethyl protecting group as a **reversible linker for purification and analysis of chemically and enzymatically synthesized nucleic acids.**

Hence, those of skill in the art are well- aware of various uses of reversibly linked biomolecules in DNA sequencing, DNA diagnostics, nucleic acid amplification, Polymerase and Ligase Chain Reactions (PCR, LCR), hybridization experiments and solid phase biochemistry. Based on the teachings and

guidance in specification and the knowledge of those of skill in the art, one can readily select those compositions that are used in these contemplated methods.

The amount of direction and guidance presented, teachings in the specification and presence of working examples

The specification describes the claimed compositions as discussed above. The two biopolymers are further described in the specification e.g., page 5, lines 14-16; insoluble supports are described at, e.g., page 5, lines 17-26; and reversible linkages are defined at, e.g., page 7, lines 19-20, page 8, lines 13-15 and 21-27, page 9, lines 1-18. Exemplary use of the claimed compositions in Ligase Chain Reaction (LCR) and Polymerase Chain Reaction (PCR) is illustrated in the specification on page 15, Example 3 (Figure 13); and page 16, Example 4 (Figure 14), respectively. Numerous articles cited in the application and attached hereto teach the use of reversibly linked biopolymers in DNA sequencing, DNA diagnostics, nucleic acid amplification, Polymerase and Ligase Chain Reactions (PCR, LCR), hybridization experiments and solid phase biochemistry. Therefore, the application provides sufficient guidance for one of skill in the art to make and use the full scope of the claimed subject matter.

CONCLUSION

In light of the scope of the claims, the description in the application, the high level of skill of those in this art, and the extensive knowledge of those of skill in this art, it would not require undue experimentation to make and use the full scope of the claimed compositions and methods. Therefore, the specification is enabling for the full scope of the claimed compositions and methods.

Rebuttal to Specific Arguments in the Office Action

1). Possession of the claimed subject matter

It is alleged in the Office Action that the specification cannot be found to enable the use of the claimed compositions when one does not have the requisite starting materials. It is urged that in order to use the claimed

composition, one must possess them. The Office Action alleges that one cannot prevail that one is enabled for the use of a composition when they do not possess it.

It appears that the Office Action is linking the enablement rejection to the written description rejection. Applicant respectfully submits that as discussed above, the specification provides adequate disclosure to prove the possession of the claimed compositions and methods. The Examiner is reminded that possession does not mean physical possession but appreciation. Further, as discussed above the application discloses use of the claimed compositions in Ligase Chain Reaction (LCR) and Polymerase Chain Reaction (PCR) on page 15, Example 3 (Figure 13); and page 16, Example 4 (Figure 14), respectively.

2). Useless biopolymers Vs. those that do have some practical utility

The Office Action alleges that the disclosure does not teach in sufficient detail how the skilled artisan is to discriminate between the useless biopolymers and those that do have some practical utility. The Office Action concludes that not knowing which biopolymer compositions are useful, the method in which they are used and how to practice that method, would result in undue experimentation.

It appears that the Office Action is using the terms "biopolymers" and "biopolymer compositions" interchangeably. Applicant respectfully submits that the claims are directed to compositions comprising biopolymers reversibly linked to insoluble supports in a particular linked arrangement. As discussed above, all the biopolymers capable of forming the reversible linkages within the scope of the claimed compositions are contemplated for use in the claimed compositions. A skilled artisan based on the specification disclosure and the knowledge available in the art would know which biopolymers are useful in forming such linked arrangements because the application describes and exemplifies such compositions. Further, the application provides exemplary embodiments where the claimed compositions are used in Ligase Chain Reaction (LCR), see, e.g.,

specification page 15, Example 3 (Figure 13) and in Polymerase Chain Reaction (PCR), see, e.g., page 16, Example 4 (Figure 14). As discussed above, the level of skill in the art is high and there is extensive literature in the art to demonstrate how to use such compositions in other methods. Therefore, it would not require undue experimentation to practice the claimed subject matter.

REJECTION OF CLAIMS 1, 2, 3, 5, 6-13, 56 and 57 UNDER 35 U.S.C. §103(a)

Claims 1, 2, 3, 5, 6-13, 56 and 57 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Köster (US Patent 6,225,450 B1) in view of Cook *et al.* (US Patent 5,543,507). The Office Action alleges that it would have been obvious to one of ordinary skill in the art to have incorporated the use of a trityl derivative linking means as disclosed by Cook into the composition of Köster because it would have allowed the artisan to selectively remove a complex from solution as well as a reversible means to then purify the composition from the insoluble supports as desired. The Office Action concludes that a person of ordinary skill in the art would have been motivated to do so as a result of a reasonable expectation of success emanating from the detailed guidance provided. Applicant respectfully traverses this rejection.

The relevant law

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious

unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The instant claims

Claim 1 is directed to compositions comprising two biopolymers, where a first biopolymer is reversibly linked to an insoluble support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality. Dependent claims 2-4 define the biopolymers as nucleic acids and polypeptides. Dependent claims 11-12 further define the nucleic acids and polypeptides. Dependent claims 6-10 define various insoluble supports used in the claimed compositions. Dependent claim 57 defines the first biopolymer as being selected from nucleic acid, enzyme, receptor and peptides.

The teachings of Köster (U.S. Patent 6,225,450 B1)

Köster '450 teaches the reversible immobilization of biopolymers such as nucleic acids, to any of a variety of solid supports via a "reversible linkage such as a photocleavable bond". This reference also teaches the solid supports suitable whereby the biopolymer would be reversibly bound in an array format.

Köster '450 does not teach or suggest the reversible binding of a second biopolymer to that of the first biopolymer whereby the first and the second biopolymers are reversibly linked to one another by a chelate complex or a photocleavable functionality.

The teachings of Cook *et al.* (U.S. Patent 5,543,507)

Cook '507 is directed to covalent cross linkages for oligonucleotides wherein a first polynucleotide is cross-linked to a second polynucleotide by a heterobifunctional trityl derivative.

Cook '507 does not teach or suggest reversible binding of the first biopolymer to insoluble support by trityl linkage.

ANALYSIS

The Office Action fails to establish that the instant claims are *prima facie* obvious over Köster in view of Cook *et al.* for the following reasons.

The combination of teachings of Köster '450 with the teachings of Cook *et al.* '507 does not result in the instantly claimed compositions.

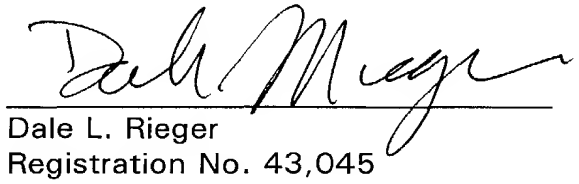
Köster '450 teaches the reversible immobilization of biopolymers such as nucleic acids, to any of a variety of solid supports by photocleavable bond. Köster '450 does not teach or suggest the reversible binding of a first biopolymer to insoluble support by a trityl linkage. Nor does Köster '450 teach or suggest a second biopolymer reversibly linked to the first by a chelate complex or a photocleavable functionality. Cook '507 does not cure this defect. Cook '507 teaches a first polynucleotide cross-linked to a second polynucleotide by a heterobifunctional trityl derivative. Cook '507 does not teach or suggest a first biopolymer reversibly linked to a second biopolymer by a chelate complex or a photocleavable functionality nor does it teach or suggest reversible linking of the first biopolymer to an insoluble support by a trityl linkage. Nor does Cook '507 teach or suggest modification of the composition of Köster to arrive at the composition of the instant claims. The combination of the teachings of Köster '450 and Cook '507 does not teach or suggest compositions comprising two biopolymers, where a first biopolymer is reversibly linked to an insoluble support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a

chelate complex or a photocleavable functionality. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness, and the rejection should be withdrawn.

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: 
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KÖSTER *et al.*	)
		)
Serial No.:	09/355,705	)
		)
Confirmation No.:	6820	)
		)
Filed:	November 5, 1999	)
		)
For:	A REVERSIBLE STOICHIOMETRIC PROCESS FOR CONJUGATING BIOMOLECULES	)
		)
Art Unit:	1634	)
		)
Examiner:	Sisson Bradley L.	)

ATTACHMENTS TO THE AMENDMENT

The following attachments are provided:

(1) Marked up paragraphs and claims in accordance with 37 CFR §1.121; and

(2) a Supplemental Information Disclosure Statement.

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MARKED UP CLAIMS (37 CFR §1.121)

Please amend claims 1, 4, 20, 23-25 and 57 as follows:

1. (Amended Four Times) A composition, comprising two biopolymers, wherein:

the first biopolymer is linked to an insoluble support by a reversible linkage; and

the second biopolymer is linked to the first biopolymer by a reversible linkage, wherein the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is [formed through a trityl derivative,] a chelate complex or a photocleavable functionality.

4. (Amended Three Times) The composition of claim 1, wherein the two biopolymers are comprised of a nucleic acid and a [protein] polypeptide.

20. (Amended Three Times) A method for preparing the composition of claim 1, comprising the steps of:

a) immobilizing a first biopolymer onto an insoluble support via a first reversible linkage; and

b) conjugating the first biopolymer with to a second biopolymer via a second reversible linkage, wherein the linkage between the insoluble support

and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is [formed through a trityl derivative,] a chelate complex or a photocleavable functionality.

23. (Twice Amended) The method of claim 22, wherein the [first or] second reversible linkage is formed by the reaction of a nucleic acid containing a chelate functionality with a polypeptide containing an imidazolyl functionality in the presence of a metal ion.

24. (Twice Amended) The method of claim 22, wherein the [first or] second reversible linkage is formed by the reaction of a nucleic acid containing an imidazolyl functionality with a polypeptide containing a chelate functionality in the presence of a metal ion.

25. (Twice Amended) The method of claim 20, wherein the [first or] second reversible linkage is formed from functionalities or precursors, which are introduced into the nucleic acid during enzymatic synthesis.

57. (Amended) A composition, comprising two biopolymers, wherein:

the first biopolymer is linked to an insoluble support by a reversible linkage; and

the second biopolymer is linked to the first biopolymer by a reversible linkage, wherein the first biopolymer is selected from a nucleic acid, enzyme, receptor and peptide; and

the linkage between the insoluble support and the first biopolymer is a trityl linkage and the linkage between the first biopolymer and the second biopolymer is a chelate complex or a photocleavable functionality.